SCIENCE

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EXPERIMENTAL AND CHEMICAL STUDIES OF THE BLOOD WITH AN APPEAL FOR MORE EXTENDED CHEMICAL TRAINING FOR THE BIOLOGICAL AND MEDICAL INVESTIGATOR. II

THE BLOOD AND THE SPECIFIC SECRETORY PRODUCTS OF THE ORGANS OF INTERNAL SECRETION

In this field we touch on the one hand upon knowledge which is deeply rooted in the earliest practical experience of mankind, and on the other on the results of epoch-making clinical observations and of experimentation in scientific laboratories up to the present moment. Man has long made practical use of the fact that the removal of the sex glands at a certain age will give us the docile ox in place of the unruly bull, the easily fattened and tender-fleshed capon for the muscular and stringy cock; and human society in its various stages of development has also practised this mutilation on its individuals for various reasons, religious, economic or penal. The sale of eunuchs in Bagirmi and other parts of North Central Africa still continues, we are told, and it was only on the accession of Pope Leo XIII. in 1878 that the practise of castrating boys in order to furnish the Sistine Choir its famous adult soprano voices was discontinued.

From remote antiquity, therefore, man has known that the gonads, or sex glands, exert a marked influence on the development and structure of the body, but until recent times there has existed no valid explanation, no correct theory of their relationship to the rest of the body. It is true, there were not wanting acute minds whose attempted explanation came close to the

truth, but experimental proof was lacking. We gather from Æsop's fable that it will not do for the various members of the body to fall out with one another, and the medicine of an older time has long used the expression *consensus partium* as indicating the interrelationship of the various organs. Even in quite modern times this *consensus* of the various organs was supposed to be entirely effected through the intermediation of the nervous system, a view tersely expressed by Cuvier when he said,

> Le système nerveux est, au fond, tout l'animal, les autres systèmes ne sont là que pour le servir.

Side by side with this view of the preponderating rôle of the nervous system we find the old humoral doctrine, having obtained new support in Harvey's discovery of the circulation, struggling to prove the importance of the blood stream for the interrelationship of the organs. In 1775, Théophile de Bordeu[22] of Montpellier and later Paris, a fashionable practitioner with considerable knowledge of anatomy, propounded the doctrine that every organ lives its own life and is the source of specific chemical substances (humeurs particulières) which are yielded up to the blood and which are necessary to the integrity of the body. The idea that every organ has its own special life is repeated again and again in Bordeu's writings:

> It must be remembered that each organic part of the living organism has its own manner of existence, of acting, of feeling and of moving: each has its own particular savor, structure, external and internal make up, odor, weight, manner of growth, of expanding and contracting; each competes after its own manner and for its share in the ensemble of all the functions, in the general life; each organ, in brief, has its own life and its own functions quite distinct from all others.[23]

From the organs the blood derives a multitude of humors and "emanations" (nuées d'émanations qui composent et animent le sang).

> Comparable at bottom to fecundated white of egg, the blood (a fluid tissue which fills the vessels of the body) is animated by the semen, that is to say, it contains a certain quantity of *seminal emanations* which vivify it; it contains in the same way a portion of the bile, and also a portion of the milky juices, especially in infancy and in women at the time of pregnancy; it contains a colored part which is elaborated in the entrails; it has serosity in abundance; it contains an extract of each glandular organ which contributes its share to the emanations in which all the solid parts (of the blood) swim; a certain quantity of air; a portion of mucous substance. . . .[24]

Bordeu's theories in respect to the diseases that are consequent to a superabundance or wrong admixture of these various special principles or emanations, his various cachexias (cachexie bileuse, albumineuse, etc.) can not be considered here.

Three quarters of a century after Bordeu, in 1849, we find a German professor of physiology, in Göttingen, A. A. Berthold, giving the first experimental proof of the correctness of this theory. This experimenter, in a beautifully concise monograph of only four pages, describes his experiments upon young cockerels. By removing the sex glands from their normal position and transplanting them to another part of the body (to the outer surfaces of the intestine in the peritoneal cavity) where it was impossible for them to expel a secretion or to play any external rôle as sex glands, he was able to prove that these glands have two functions: (*a*) the well-known reproductive function, and (*b*) an important function in maintaining, as he says, the "*consensus partium.*" Such cockerels did not show the changes that were seen in the castrated bird; on the contrary, they developed into the usual type, remaining male birds in respect to their vocal capacity,

22 See his "Recherches anatomiques sur la position des glandes et sur leur action," Paris, 1752; and his "Analyse médicinale du sang," 1776.

23 P. 942, "Analyse médicinale du sang," Vol. 2, "Œuvres complètes de Bordeu," edited by Richerand, Paris, 1818.

24 P. 1,006, *ibid.*

their desire for battle, the growth of comb and wattles and the sexual instinct. Berthold draws the conclusion from his experiments that the generative organs influence the *consensus partium* by acting upon the blood and through this upon the organism as a whole.

The observations of Berthold were forgotten and even discredited (Rudolf Wagner) and they had no influence apparently on the development of work in this field during the following half century.

I can not leave this part of my subject without mentioning the work of the great Frenchman, Claude Bernard, whose discovery of glycogen in the liver and elsewhere must always rank as one of the great discoveries of physiology. With perfect justice Bernard declared that the conversion of glycogen into sugar and the passage of the latter into the blood constitutes the internal secretion of the liver, while the bile constitutes its external secretion.

One other investigator, the modern pioneer in this field, a restless spirit, a man of enthusiasms, possessing an original mind of a high order, one who is of especial interest to Americans, can not be passed by without mention. Charles Edward Brown-Séquard was born at Port Louis, Mauritius, on April 8, 1817. His father was an American, his mother a French woman, but he himself, it is stated, always wished to be regarded as a British subject. After a varied career in four countries (England, France, Mauritius and the United States) having held the chair of physiology in Harvard from 1864 to 1867, he finally, in 1878, succeeded Claude Bernard as professor of experimental medicine in the Collège de France, where he remained until his death in 1894.

As far back as 1869 Brown-Séquard took the position in his lectures in Paris that all glandular organs, irrespective of whether they possess external excretory ducts or not, give off to the blood substances which are useful and necessary for the body as a whole, an opinion, as we have seen, that had already been stated by Théophile de Bordeu in 1775. He even made experiments on himself with a testicular extract, and the meeting of the Paris Societé de Biologie, June 1, 1889, at which Brown-Séquard, then 72 years old, made his report on these experiments, Biedl calls "the true birthday of the doctrine of internal secretion."

From this time an ever-increasing army of experimental laboratory workers have been engaged in this field. Their names even can not here be given, neither can I go into detail with regard to the great and fundamental contributions that have been made by medical clinicians, surgeons and anatomists, as Basedow, Graves, Addison, Marie, Gull, Ord, Kocher, Reverdin, Minkowski, Von Mering, Sandström and others, to name only some of the leaders of the immediate past, not to speak of the excellent contributions that have been made in recent years by our own surgeons and internists.

And so there has gradually come into existence an enormous store of facts, physiological, pathological, chemical and clinical, in regard to a number of structures that are classed as endocrinous glands or organs of internal secretion.

What is meant to-day by this term, products of internal secretion, and what organs furnish principles that can be classed as internal secretions?

For the present we shall follow custom and apply the term *to definite and specifically acting indispensable chemical products of certain organs* (*organs that may or may not have an external secretion*), *which are poured into the blood and modify the development and growth of other organs,*

more especially during embryonic and early life, and which also greatly affect the entire metabolism, that of the nervous system included, during adult life. I regard it as not unlikely that with the growth of knowledge of the chemistry of the animal organism we shall drop the term entirely. We have already seen that the liver, according to Claude Bernard's view, has an internal secretion, yet this gland is not usually classed with the endocrinous organs. In a sense, too, as has been frequently pointed out, every cell of the body furnishes in the carbon dioxide which it eliminates a hormone or product of internal secretion, since under normal conditions the carbon dioxide of the blood is one of the chief regulators of the respiratory center, influencing this center by virtue of its acidic properties. These and other instances that could be given show that the term internal secretion could be greatly extended in its scope, but in the present state of our knowledge it is convenient to limit it to the products of a certain number of glands.

The generally accepted list of the organs of internal secretion is as follows, though even at this moment a foreign investigator[25] is asking us to accept certain newly discovered small structures located in the neck as belonging to our list: the thyroid, parathyroid, thymus, hypophysis cerebri, epiphysis cerebri, pancreas, mucosa of the duodenum, the two adrenal systems (the chromaphil tissue and the interrenal bodies) and the gonads, or sex glands.

Permit me to give you a few illustrations of the derangement of health and bodily structure that follow upon the removal or disease of these glands. Many of you have doubtless seen these illustrations, but I am giving them here for the benefit of those who have never been given proof of the great significance of these glands in order that they may have a background of fact for the better apprehension of certain chemical questions which I wish presently to bring to your notice.

The figure[26] is an illustration from a well-known paper of the Viennese surgeon, A. v. Eiselsberg, in which he describes the effects of removing the thyroid gland from young goats. The two animals here shown are of the same age and parentage. On the twenty-first day after birth v. Eiselsberg removed the thyroid gland from one of them. The incision healed by primary intention. After three weeks the control animal began to outgrow the one operated upon and when four months old the animals presented the appearance here shown. The goat with thyroid removed has shortened extremities, a shortened skull and an altered pelvis due to a delayed ossification at the epiphyseal line. The wool of this animal is longer and easily torn out by the handful, the sex glands are atrophied, the hypophysis is enlarged, the intelligence is lowered; in brief, a chronic pathological condition is produced in this experiment which finds an analogy in human beings and is known as *cachexia thyreopriva.* We can not enter into further details, but I may remark that the results obtained in such removal experiments vary greatly with the age and with the species of animal used.

In this figure we have the results of a similar experiment which nature herself has performed for us. The child here shown is a thirteen-year-old idiotic myxedematous dwarf whose general symptoms point to a congenital absence of the thyroid gland. Investigators have proved this to be the true cause by anatomical studies of the

[25] "Ueber eine neue Drüse mit innerer Sekretion (Glandula insularis cervicalis)," N. Pende, *Arch. f. mikroscop. Anat.*, Vol. 86, p. 193, 1914.

[26] The illustrations were shown in the lecture, but can not here be reproduced.

bodies of other congenital myxedematous children of this class.

Further illustrations were then given by means of lantern slides of endemic cretinism and goiter and it was shown by statistics and by a map of Europe that these abnormalities have very great economic significance, on account of their great prevalence in certain parts of central and western Europe and to a less degree in our own and other countries. For instance, in Switzerland one sixth of the male population is unfitted for military service by cretinism in some degree.[27]

After even these few illustrations of abnormalities that follow on removal or disease of these glands, I think you will agree with me that my colleague, Professor Barker, has not exaggerated their importance when he says,

More and more we are forced to realize that the general form and the external appearance of the human body depend to a large extent upon the functioning, during the early developmental period (and later), of the endocrine glands. Our stature, the kinds of faces we have, the length of our arms and legs, and the shape of the pelvis, the color and consistency of our integument, the quantity and regional location of our subcutaneous fat, the amount and distribution of hair on our bodies, the tonicity of our muscles, the sound of the voice and the size of the larynx, the emotions to which our *exterieur* gives expression—all are to a certain extent conditioned by the productivity of our hormonopoietic glands. We are simultaneously, in a sense, the beneficiaries and the victims of the chemical correlations of our endocrine organs.[28]

I can not here take up questions of therapeutics in this interesting field. I can only say that *aside* from surgical intervention and the brilliant results of thyroid treatment in cases once utterly hopeless, we have little to offer that has been *positively* established. Nor shall I attempt to discuss the interrelationship of these glands. It has become increasingly evident that to touch one of them is to touch all. Various writers have endeavored to express this interrelationship in a series of charts or diagrams. Of these diagrams D. Noël Paton has well said:[29]

They may well be a grotesque parody of what will ultimately be found to be the relationship of the activities of these organs. They are probably as near the truth as those quaint ancient maps of the Indies with their "here be gold" scrawled across them which served as the charts of our forefathers, and if, like them, they merely indicate the direction which further investigation should take and suggest lines of attack, they will have served their purpose.

Notable and well established, apparently, is the relationship existing between the gonads, the thyroid and thymus glands, the hypophysis and suprarenal glands. Very difficult is it also to unravel the relationship of the internal secretions as a whole to the nervous system, both central and peripheral.

In view of the fact that we so little understand the chemical principles elaborated in these organs and discharged by them into the blood, whereby the remarkable changes described above are effected, it is evident that further progress now waits on chemical discoveries.

[27] "Der Kretinismus," H. Vogt, in *Handbuch der Neurologie* (Lewandowsky), Vol. IV., Spezielle Neurologie, III., p. 139. Here also it is stated that the three Italian provinces, Piedmont, Lombardy and Venice had 120,000 cases of goiter and 13,000 cretins in 1883, the total population of these provinces at that time being 9,400,000. In 1908, according to Biedl, Austria had on the average 64 cretins to every 100,000 of the population. In 1873 France had 120,000 cretins in Savoy, the Maritime Alps and the Pyrenees. It will be seen that the thyreopathies constitute a heavy drain on the resources of European people.

Pictures of persons suffering from other disorders, as exophthalmic goiter, acromegaly or giantism and parathyroid tetany, were also given with a brief statement of the glandular and general nutritive changes involved. Animals such as the monkey, the dog, the rat and others are likewise subject to disease of this gland.

[28] "On Abnormalities of the Endocrine Functions of the Gonads of the Male," *Am. Jour. Med. Sciences*, Vol. 149, p. 1, 1915.

[29] "Regulators of Metabolism," p. 183. Macmillan & Co., London, 1913.

The only fairly complete chemical work yet done on any of these organs is that on the suprarenal glands. These organs are two flattened, ductless, yellow-brown glands, each of which is loosely attached to the anterior and inner part of the summit of the corresponding kidney. The normal gland of a healthy man weighs, according to Elliott,[30] between four and five grams, and contains four or five milligrams of the characteristic principle concerning which I shall speak in a moment. These organs are essential to life; their destruction in man by tubercular and more rarely by other processes leads to a chronic condition characterized by gastro-intestinal symptoms, great muscular weakness and a bronzing of the skin and mucous membranes, this whole symptom complex being known as Addison's disease (1855). In man and the higher animals generally this organ is a double structure in which two parts which are quite separate and totally different in lower forms, as in the elasmobranch and teleostean fishes, are united in such a manner that one constitutes the medulla and the other the cortex of the gland, the latter completely enclosing the former.

The cortical part of the gland is called by histologists the inter-renal tissue. Biedl has shown that when this tissue is removed from selachians (where, as just stated, it constitutes a separate organ) the animal gradually weakens, no longer takes food and dies in fourteen to eighteen days. Still other experiments demonstrate that this cortical part of the gland exerts great influence on bodily growth and sexual development. Numerous researches of a chemical character have been carried out on this part of the gland, especially in respect to its lipoid content. Last year Voegtlin and Macht[31] isolated from it and also from blood serum a new crystalline substance which has a vaso-constricting action on the blood vessels and a digitalis-like action on the heart. This has been decided to be a lipoid closely related to cholesterin. As we are entirely ignorant of the means by which the adrenal cortex exerts its profound influence on the body, the isolation of this substance is of especial interest. For the present we can not state whether it represents one or all of the products of the internal secretion of the cortex, or whether, indeed, it has any connection at all with the function of the gland.

The medullary portion consists of cell groups which assume a brown color when treated with chromic acid or dichromates, in consequence of the reduction of these compounds to brownish or reddish-brown basic chromates. For this reason it has been designated the chromaphil tissue. Now such chromaphilic cell groups are not confined to the medulla of the suprarenal gland, but are also found lying alongside the abdominal aorta, in the carotid gland and in the sympathetic system.

It was known to earlier experimenters that aqueous extracts of the entire capsules were highly toxic to animals when injected directly into the circulation, but it remained for Oliver and Schäfer in 1894 to demonstrate that extracts of the medullary part, in the most minute quantity, cause a marked rise in blood pressure and greatly stimulate the heart. In 1897 I showed that the substance responsible for these actions could be isolated from the glands in the form of a benzoyl compound.[32] Salts of a

[30] "Death and the Adrenal Gland," *Quar. Jour. of Medicine*, Vol. 8, p. 47, 1914. An interesting paper by E. R. Weidlein, a fellow of the Mellon Institute, on the adrenal glands of the whale will be found in the *Jour. of Industrial and Engineering Chemistry*, Vol. 4, No. 9, September, 1912.

[31] "Isolation of a New Vasoconstrictor Substance from the Blood and the Adrenal Cortex," *Jour. Amer. Med. Assoc.*, Vol. 61, p. 2,136, 1913.

[32] For literature see Abel and Macht, *Jour. of*

base obtained by saponifying this benzoyl derivative were shown by me (1898) to possess the characteristic chemical and physiological properties of the gland itself. To the principle thus isolated I gave the name epinephrin. Very soon after this v. Fürth (1899–1900) isolated the principle under discussion in the form of an amorphous indigo-colored iron compound, and in 1901, Takamine and Aldrich succeeded independently in precipitating the native substance with the help of ammonia, and without first subjecting it to the more complicated processes which had been used by myself some years before.

These results were soon followed by the brilliant researches of a number of organic chemists, Dakin, Jowett, Pauly and Friedmann, which culminated in the synthetic production, first, of the racemic form by Stolz in 1906, and later of the levorotatory form by Flächer in 1908, the form in which the substance exists in the gland itself. The chemical history of this remarkable blood-pressure-raising constituent which is found wherever chromaphil tissue is encountered is therefore now a closed chapter. We are no longer dependent upon the glands of the ox or the sheep for its preparation for the many uses to which it is put by the medical specialist, the surgeon and the general practitioner, but shall always be able to produce it in our laboratories as long as coal-tar remains at our disposal. In chemical language it is described as a di-hydroxymethyl-aminoethylol benzene, or more concisely and simply, it is an aromatic amino alcohol. It is as noteworthy for its instability in solution as it is remarkable for its physiological properties. It is a true product of internal secretion and can apparently be detected in the venous blood of the adrenal glands.[33] I shall not further describe its chemical properties, but would call your attention to the fact that in at least one animal, a tropical toad, *Bufo agua,* this principle occurs also as a constituent of an external secretion.

Pharmacol. and Exp. Therapeutics, Vol. 3, p. 327, 1912.

The toad, I may say here, has a very interesting history.[34] It has been regarded from the earliest times as a poisonous animal and various races, including our own, have long made medicinal use of its skin. The Chinese to this day use as a cure for dropsy a preparation derived from toad skin, called *senso.* Among western nations it has always been a folk's remedy, and almost up to the time of the introduction of digitalis (1775) as a medical agent our very best medical authorities used these skins in cases of dropsy. Dr. Langworthy, Department of Agriculture, Washington, has given me the following recipe for making a toad ointment which was in use among our early New England colonists for the treatment of sprains and rheumatism. Toad ointment: good-sized live toads, 4 in number; put into boiling water and cook very soft; then take them out and boil the water down to one half pint, and add fresh churned, unsalted butter 1 pound and simmer together; at the last add tincture of arnica 2 ounces.

The particular toad, *Bufo agua,* to which I have referred, is of further interest because the aborigines of the Upper Amazon make an arrow poison from the creamy secretion that exudes from its skin glands when it is irritated or overheated, a poison

33 It has not been conclusively shown that the blood-pressure-raising constituent of this blood is really epinephrin (adrenalin) and not an alteration product.

34 Abel and Macht, "The Poisons of the Tropical Toad, *Bufo agua,*" *Jour. Amer. Med. Assoc.,* Vol. 56, p. 1,531, 1911, and "Two Crystalline Pharmacological Agents obtained from the Tropical Toad, *Bufo agua,*" *Jour. Pharmacol. and Exp. Therapeutics,* Vol. 3, p. 1,319, 1912.

so powerful that it kills in a few moments large game, such as the stag or the jaguar.

Two years ago I was examining a specimen of this giant among toads when I noticed that this creamy secretion made on a scalpel a peculiar, greenish-blue discoloration. I at once remembered where I had seen this color years before on a scalpel used in cutting into the medulla of a suprarenal gland. Working from this hint, I was soon able to isolate the now familiar substance, adrenalin or epinephrin, from this toad's glands. Scientists have been not a little surprised to learn that this substance is present in very large amounts in the skin of this tropical toad. It is not found in the skin of the common American toad.

I also succeeded in isolating the principle to which the toad skin owes its curative power for dropsy, a very different principle from epinephrin. It has been obtained in the form of beautiful crystals and has the composition represented by the formula, $C_{18}H_{24}O_4$, and has been named bufagin.

Just as in the case of bleeding, we have here another instance of the every-day observation of mankind justified by science. That powdered toad skin could cure dropsy has been ridiculed by the learned for a century, and now we possess in bufagin and in the slightly different bufotalin, which has only recently been obtained in crystalline form from the skin of the common European toad, the actual proof of the correctness of the old belief.

We are now studying the chemical constitution of bufagin in my laboratory, and although this problem is one of great difficulty, we hope, nevertheless, that our work will throw some light on the fundamental chemical properties of cardiac stimulants. We now also understand why the secretion of the skin of *Bufo agua* may be used as an arrow poison, since it contains these two powerful drugs, epinephrin and bufagin, which in overdose act fatally on the heart and blood vessels.

We can not leave the consideration of this subject without noting the influence that the study of the pharmacological properties of epinephrin has exerted on certain departments of medical science.

Chromaphilic cells of the body, whether located in the medullary portion of the suprarenal gland, or elsewhere, all yield epinephrin, and modern studies have shown that these chromaphilic cells are intimately related to the sympathetic nervous system in their origin, and have differentiated themselves from it. We are not surprised, therefore, to find that epinephrin, the secretory product of these cells, has an elective affinity for the sympathetic nervous system, the thoracico-abdominal part of the autonomic system. The well-known symptoms that follow upon the administration of epinephrin, extreme vaso-constriction, tachycardia, dilatation of the pupil, inhibition of peristaltic movement in the alimentary canal, contraction of the pyloric and ileo-cecal sphincters, increased motility of the pregnant uterus and glycosuria have all been shown to be due to the fact that this hormone stimulates and sensitizes the sympathetic myoneural and adenoneural junctions or terminations of the sympathetic nervous system. Numerous experiments have shown that the changes induced by epinephrin in the activity of various organs which are innervated by the sympathetic nervous system are in all respects like those that are brought about by electrical stimulation of this system, and it is apparent that such experiments have already assisted in elucidating many obscure points in the functional activity of this part of the nervous system.

Other interesting observations which deal with the action of this principle upon

the metabolism of the body or with the pathological changes induced by toxic doses can not be taken up here.

The discovery of the chemical structure and pharmacological properties of epinephrin has greatly encouraged investigators to take up the isolation of other active principles. Thus Abelous[35] and his coworkers showed that the intravenous injection of extracts from putrid meat caused a rise of an animal's blood pressure. Barger and Walpole[36] then proved that this effect was due to the presence of isoamylamine, phenyl-ethylamine and para-hydroxyphenylethylamine.

These amines are produced by putrefactive bacteria from proteids, and they exhibit pressor or blood-pressure-raising effects that in general are very similar to those produced by epinephrin. A close similarity in chemical structure of two of these amines, phenyl-ethyl-amine and para-hydroxyphenylethylamine, to epinephrin is shown in the graphic chemical formulæ which will presently be given. The last-named base is of special interest to us, since Barger has discovered that it is also present in ergot and is in some degree responsible for the characteristic activities of this drug. It is also present to a small extent in Emmenthaler cheese. More remarkable still is the discovery of Henze that this amine is the effective principle of a highly active poison produced by the posterior, so-called salivary glands of a certain cephalapod found in the Bay of Naples. It has long been known that this mollusc renders its prey, as the crab, quickly helpless by means of this poison and until Henze's discovery it was believed to be a toxalbumin.

We find, therefore, that p-hydroxyethylamine is produced by putrefactive bacteria, that it is present in ergot (the permanent mycelium of the fungus, *Claviceps purpurea*), and that it is the product of the metabolism of a glandular tissue. In each case it may be assumed that it is obtained by chemical reactions from the protein molecule, its immediate precursor being the innocuous tyrosin.

By merely splitting off a molecule of CO_2 from tyrosin, as was demonstrated by Barger, we at once secure this amine, as shown by the accompanying formulæ. As a recent writer has remarked, "Our poisons and our drugs are in many instances the close relatives of harmful compounds that represent the intermediary steps in the daily routine of metabolism."[37]

The fact that putrefactive microorganisms can produce poisonous amines by decarboxylating the harmless amino-acids has become of the highest importance to medicine. It would appear that we have at last got onto the right road for the chemical investigation of alimentary toxemia and its alleged consequences, such as arteriosclerosis and chronic renal disease. Phenylalanine, tyrosine, tryptophane and histidine, the harmless precursors of toxic amines, are always present in the intestine, and when they are acted upon by an excessive number of certain microorganisms the resulting toxic bases will surely be formed in excess. If they are then taken up into the blood in quantities too large for transformation by the liver, or other defensive organs, into less harmful derivatives they must inevitably manifest their pharmacological and toxicological properties. Let me give but one further example of recent advances in this field. It has been shown by Barger and Dale[38] that the highly poi-

[35] *Compt. rend. Soc. de Biol.*, Vol. 58, I., pp. 463 and 530 (1906), Vol. 64, p. 907, 1908.

[36] *Jour. of Physiol.*, Vol. 38, p. 343, 1909.

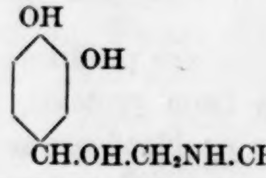
[37] *Jour. Amer. Med. Assoc.*, editorial comment, Vol. 62, January 3, 1914.

[38] *Jour. of Physiol.*, Vol. 40, p. 1,910; Vol. 41, p. 499, 1910–11. Consult also the work of Ackermann, who first demonstrated that when pure his-

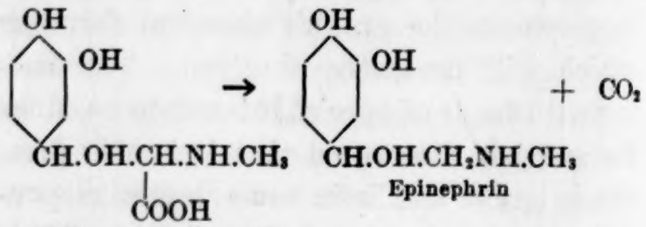
sonous depressor base, β-imino-azolylethylamine may be isolated from the intestinal mucosa, and Berthelot and Bertrand[39] have demonstrated that it is in all probability formed in the intestinal canal from histidine by the decarboxylating action of a bacillus newly discovered by them which they have named *Bacillus aminophilus intestinalis.* These investigators have shown that their bacillus produces the base from histidine even in the presence of 0.3 per cent. lactic acid, unless, indeed, an excess of glucose be present, in which case only this is attacked, and they have also made the interesting observation that rats, fed on a milk diet, are not affected by either *Proteus vulgaris* or *Bacillus aminophilus intestinalis* when these organisms are given separately, but that when they are given simultaneously the rats succumb to a diarrhea in from four to eight days.

Investigations on the pharmacological behavior of β-imino-azolylethylamine have shown that it acts very powerfully on plain muscle, stimulating the isolated uterus, for example, to contraction in the almost unbelievable dilution of 1:250,000,000.[40] The muscular coats of the guinea-pig's bronchioles are so sensitive to its action that large pigs are killed in a few minutes by the intravenous injection of a half a milligram. The death of the animal is due to asphyxia produced by a spasm of the bronchioles. Recently investigators have been much occupied in studying similar features in the symptoms of the poisoning by large doses of the base and those observed in anaphylactic shock (action on the circulation, body temperature, respiration, etc.) and some do not hesitate to affirm that the poisons of anaphylactic shock must be put into the same pharmacological class with the proteinogenous bases that we have been considering.

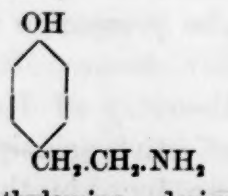
We may now give the chemical formulæ that illustrate the various relationships that have been discussed.

1. 

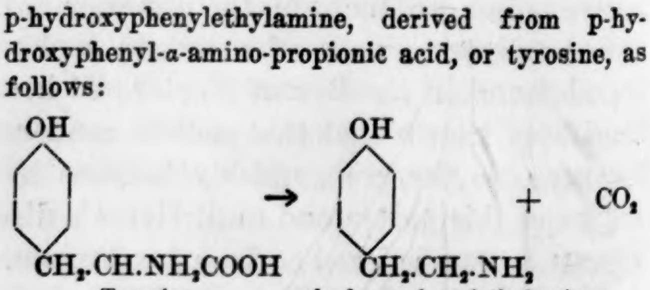
Epinephrin, adrenaline, suprarenin, possibly derived by decarboxylation from a still unknown amino acid, dioxyphenyl-α-methylamino-β-oxypropionic acid, as suggested by M. Guggenheim. *Therap. Monatsh.*, XXVII., p. 508, 1913.



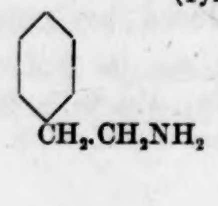
(Unknown amino-acid) Epinephrin

2. 

p-hydroxyphenylethylamine, derived from p-hydroxyphenyl-α-amino-propionic acid, or tyrosine, as follows:



Tyrosine p-hydroxyphenylethylamine (Tyramine)

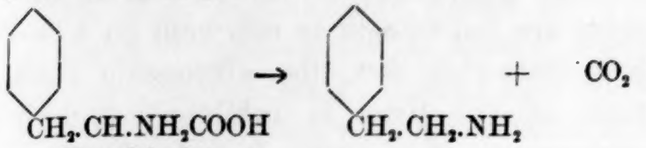
3. 

tidine is submitted to the action of putrefactive bacteria a considerable yield of β-imino-azolylethylamine is produced. *Ztschr. f. physiol. Chem.* Vol. 64, p. 504, 1910.

[39] *Compt. rend. de l'Acad. des Sciences,* Vol. 154, pp. 1,643 and 1,826. See also Mallenby and Twort, "On the Presence of β-imino-azolylethylamine in the Intestinal Wall, with a Method of Isolating a Bacillus from the Alimentary Canal which Converts Histidine into this Substance," *Jour. of Physiol.*, 45, p. 53.

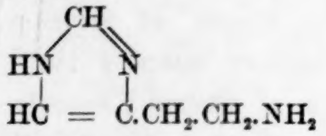
[40] See Fröhlich and Pick, *Arch. f. Exp. Pathol. u. Pharmakol.*, Vol. 71, p. 23, and Sugimoto, *ibid.*, Vol. 74, p. 27.

Phenylethylamine, derived by decarboxylation from phenyl-α-amino-propionic acid or phenylalanine, as follows:

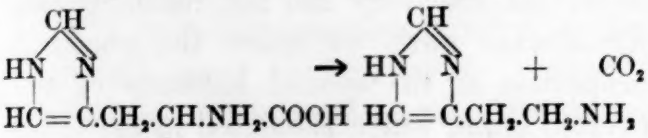


Phenylalanine

4.



β-Imidoazolylethylamine, histamin, obtained by decarboxylation of histidine, as follows:



IV. I come now to the concluding portion of my address. That science in general is a basic fact in the development of commerce and industry seems to be fully appreciated in this city, as shown by the establishment of the Mellon Institute of Industrial Research and School of Specific Industries, through the munificence of two of your public-spirited citizens, the Messrs. Richard B. and Andrew W. Mellon. I believe that no act of their lives will give them more enduring satisfaction than this which marks out your city as one more great center of industry which acknowledges the dependence of all advance in material civilization on the quiet labors of the investigator. This dependence has been forcibly expressed by former ambassador James Bryce in an address to the members of the National Academy of Sciences.

> You men of science are really the rulers of the world. It is in your hands that lies control of the forces of activity; it is you who are going to make the history of the future because all commerce and all industry is to-day far more than ever the child and product of science. . . . It is in your hands that the future lies, far more than in those of military men or politicians.

Let me also in this connection recall the inspiring words of that great investigator and benefactor of mankind, Louis Pasteur, which point out the still wider influence of science. He wrote:

> Laboratories and discoveries are correlative terms; if you suppress laboratories, physical science will be stricken with barrenness and death, it will become mere powerless information instead of a science of progress and futurity; give it back its laboratories, and life, fecundity and power will reappear. . . . Ask that they be multiplied and completed. They are the temples of the future, of riches and of comfort. There humanity grows greater, better, stronger. There she can read the works of nature, works of progress and universal harmony, while humanity's own works are too often those of barbarism, of fanaticism and destruction.

And here I shall permit myself to speak more specifically of the paramount importance of chemistry in biological and medical research. The subjects to which I have been calling your attention to-night, viz., the still unknown chemical properties and molecular structure, with the single exception of epinephrin, of the mysterious, correlating substances stored and formed in the many organs of internal secretion, and the equally unknown character of numerous constituents of the circulating blood, both offer a virgin field to the biologist with a chemist's training.

The practical importance of decisive chemical advances along this line are hardly to be overstated. At present we meet only vast confusion and contradictory theories. A single clean-cut discovery, the separation from another of these glands of a definite chemical individual shown to possess one or more of the specific actions of the gland would clear away the mists at once, and we should see the same rapid progress that has followed the isolation of epinephrin, which is only one, and perhaps not the most important, constituent of the suprarenal gland.

What a flood of light was thrown on the whole question of carbohydrate metabolism

in the discovery by Claude Bernard of glycogen in the liver! Innumerable fruitful researches have come from this as a starting-point, and their bearing on our understanding of such diseases as diabetes mellitus has been of the most fundamental nature.

Miescher's discovery of the existence of protamin nucleate in the spermatozoan heads of the Rhine salmon is another case of the far-reaching importance of a definite chemical fact for both biology and medicine. For further discoveries in the field of nucleinic acids, a later worker, Professor Kossel, received the Nobel prize. To name only one practical outcome of these discoveries, our theories of the origin of uric acid in gout and of the purins in general have undergone entire transformation.

The actual finding of definite and specific chemical principles in the organs of internal secretion has in each case an importance in the way of explaining and correlating a large number of disconnected facts, only to be likened to the discovery of the etiological cause of an infectious disease. The bacilli of tuberculosis or of typhoid, or the protozoa of syphilis and sleeping-sickness, are illuminating examples in point. Here, too, simplicity at once took the place of what had been confused and complex, and a multitude of already recorded facts fell into their proper place.

From my insistence on our ignorance of the specific secretory products of the organs of internal secretion, and of numerous constituents of the blood, it is not to be inferred that important chemical facts are lacking with regard to these tissues. On the contrary, a vast number of facts, some of immediate, others of potential significance, have been amassed by an army of workers in the past 30 years; it is their *relation to each other and to an underlying cause* which remains obscure. For example: it has been recently shown by Cramer and Krause[41] that when fresh thyroids are fed to cats or rats kept on a carbohydrate-rich diet, the glycogenic function of the liver is inhibited, and in consequence this organ is soon found to contain only traces of glycogen. And these investigators suspect that the well-known action of thyroid secretion on the metabolism is effected through this change in the carbohydrate metabolism. But this important discovery can not reach its full significance until we know the chemical properties of the special hormone of the thyroid gland which is carried in the blood to the liver and there prevents the formation of glycogen even though the food may contain an abundance of carbohydrate.

Thus, too, one of the facts known about the parathyroids, as shown by MacCallum and Voegtlin,[42] is that their removal from the body is followed by increased excretion of calcium salts. This chemical discovery also can not yet be brought into a causal connection with a definite chemical constituent of the gland.

That I may not be accused of placing too much emphasis upon only one mode of attack in biological and medical research, let me say that I am fully aware of how many-sided are all these problems, and that fundamental discoveries have been made and will continue to be made without the aid of chemistry. This is true especially in the field of morphology. But as soon as we touch the complex processes that go on in a living thing, be it plant or animal, we are at once forced to use the methods of this science. No longer will the microscope, the kymograph, the scalpel avail for the complete solution of the problem. For the further analysis of these phenomena which

41 *Proc. Roy. Soc. B.*, Vol. 86, p. 550, 1913.

42 *Jour. Exp. Med.*, Vol. 11, p. 118, 1909.

are in flux and flow, the investigator must associate himself with those who have labored in fields where *molecules and atoms, rather than multicellular tissues or even unicellular organisms, are the units of study.* To-day investigators in biology and medicine are reaching out with eager hands into the more exact branches of science. The great progress in biology and in medicine that has been made during the past century proves that advantages hardly to be imagined must follow upon the further application of physics and chemistry to these sciences. A striking example of the debt which medicine owes to that newer branch of chemistry called physical chemistry is seen in our better understanding in the last twenty years of certain dynamic equilibria of the body, such as the relationship between the hydrogen and the hydroxyl ions of the blood and tissues, of surface tension, osmotic pressure and the colloidal state.

I also recognize that all the various aspects of any one problem in our field are intimately bound together, and that progress along the chemical side, for instance, of a question may have to wait on the clearing up of the morphological side. When I have the honor of being consulted by a young man who has not yet found himself intellectually but who is filled with the desire to devote his life to some branch of medicine, be it clinical medicine, pathology, hygiene, bacteriology, physiology or pharmacology, my advice always is, "Study chemistry for at least three years. Try with all your power to master enough of this great science to start you in your career." Why not make this attempt at a time of life when one still takes kindly to a rigid discipline[43] such as this science exacts? To this preparation must be added the special medical training of another four or more years. A long road to travel? But I find that many young men have entered upon it with great enthusiasm.

I do not mean that this long tutelage is to be a cramming process. I have in mind conditions where these students shall be constantly under the influence of teachers who are themselves investigators and daily engaged in the search for new truths. Under the stimulus of such examples our young man is saved from the sterile life of the mere crammer, because he sees the relation of what he learns to living questions. During this period of study and growth he will himself make occasional attempts at the solution of problems. Even with the best preparation, workers in our fields have always to return again and again to the fundamental sciences for assistance.

But to what end is all this preparation for our young man? Is it solely that he may solve problems whose solution is of practical value to mankind? Is his mind to shape itself only to the insistent demands of utility? Even then our method of training will yield the largest profit. But it does vastly more than that. Thus trained our young scholar will be able to see beyond the immediately practical problem, even though it be as great a thing as the discovery of the cause and cure of the plague that decimates a people. *Greater even than the greatest discovery is it to keep open the way to future discoveries.* This can only be done when the investigator freely dares, moved as by an inner propulsion, to attack problems not because they give promise of immediate value to the

[43] The professor of physics in McGill University, Dr. A. S. Eve, has recently expressed himself as follows in a paper describing modern discoveries on the constitution of the atom (*Jour. Franklin Institute*, 1915, p. 269): "It may be noted that the discoveries set forth in this brief summary have been achieved by savants in the western half of Europe, and it may be asked if the education in the New World is at the present time sufficiently thorough, imaginative and philosophical."

human race, but because they make an irresistible appeal by reason of an inner beauty. Some of the greatest investigators indeed have been fascinated by problems of immediate utility as well as by those that deal with abstract conceptions only. Helmholtz invented the ophthalmoscope and thus made modern ophthalmology possible, and at the same time did work of the highest order in theoretical physics and wrote on the nature of the mathematical axioms and the principles of psychology. Lord Kelvin took out patents on great improvements in the compass and on oversea telegraphy, and also made contributions to our knowledge of the ultimate constitution of the atom and the properties of the ether. From this point of view the investigator is a man whose inner life is *free* in the best sense of the word. In short, *there should be in research work a cultural character, an artistic quality, elements that give to painting, music and poetry their high place in the life of man.*

Ladies and gentlemen, I have attempted in this hour to point out some recent advances that have been made in the study of the blood and of the organs of internal secretion, and have cited the beneficent effects of even these small advances—a very few bright stars in a darkened sky—in order to emphasize the great rôle that chemistry is destined to play in biology and medicine. I have strongly urged that those who are to be medical teachers and investigators should not content themselves with a mere smattering, but endeavor to acquire a really sound training in one of the fundamental sciences.

You, my colleagues, working with open-minded and generous trustees, must see to it that the men selected for important posts shall be those that are capable of training and inspiring the young men who in their turn will furnish the leadership of the future.

In our country many agencies combine to foster the higher learning. It is to the lasting honor of men of wealth that they have appreciated the need for institutes of research and in a number of notable instances have placed large sums at the disposal of science. They have responded nobly to that appeal of Pasteur which I have already cited in which he calls laboratories "the temples of the future, of riches and of comfort."

John J. Abel

The Johns Hopkins Medical School

CHARLES WILLIAM PRENTISS

Charles William Prentiss, professor of microscopic anatomy in the Northwestern University Medical School, died at Chicago on the twelfth day of June. Born in Washington, D. C., August 14, 1874, he spent many of his early years at Middlebury, Vermont.

His undergraduate work was done at Middlebury College, where his father, Dr. Charles E. Prentiss, was librarian. He was graduated with honors in 1896 but remained there another year as a graduate student. During the next three years he was at Harvard University in the department of zoology. Here he received the degree of doctor of philosophy in 1900. The following year was spent at the Harvard Medical School as instructor in anatomy. He was then awarded a Parker Traveling Fellowship and studied in Europe for two years. Although the greater part of this time was spent at Freiburg and Naples his work with Bethe at Strassburg had the more important influence on his career.

On his return to America he held appointments successively in the zoological departments of Western Reserve University and the University of Washington, Seattle. While in the latter place he first developed the symptoms of duodenal ulcer from which he suffered for the last eight years. He came to Northwestern University Medical School as assistant professor of anatomy in 1909 and was made professor of microscopic anatomy in 1913.

Professor Prentiss was a member of the Society of Naturalists, the Society of Zoologists and the Association of Anatomists. He was the author of many papers presenting the results of his own investigations in the fields of zoology and anatomy among the more important of which may be mentioned:

1. "The Otocyst of Decapod Crustacea," *Bull. Mus. Comp. Zool.*, 1901.

This was his thesis for the doctorate and was a well-rounded piece of histological and physiological work.

2. "Polydactylism in Man and the Domestic Animals," *Bull. Mus. Comp. Zool.*, 1903.
3. "The Neurofibrillar Structure in the Ganglia of the Leech and Crayfish with Especial Reference to the Neurone Theory," *Jour. Comp. Neur.*, 1903.
4. "The Nervous Structures in the Palate of the Frog," *Jour. Comp. Neur.*, 1904.
5. "The Development of the Hypoglossal Ganglia of Pig Embryos," *Jour. Comp. Neur.*, 1910.
6. "The Development of the Membrana Tectoria with Reference to its Structure and Attachments," *Amer. Jour. Anat.*, 1913.

Dr. Prentiss's "Text-book of Embryology" published in January, 1915, less than six months before his death, met at once with a very favorable reception. It is an example of text-book-making at its very best. The wealth of excellent illustrations and the clear concise text make it indispensable for the student of embryology. In it there are also may contributions of an original character not published elsewhere.

Professor Prentiss's scientific work was characterized by a scrupulous attention to detail and by the perfection of his technical methods. He handled with great success and on difficult material the most delicate of neurological methods—the methylene blue stain. His dexterity was shown again in remarkable dissections of embryos, drawings from which appear in his book. He brought to all his work an unusually clear mind and a keen insight into fundamental problems.

Reticent, almost shy, by nature, and prevented by the condition of his health from often joining his colleagues at the regular Christmas meetings Dr. Prentiss was intimately known to only a chosen few. To them he was endeared by reason of his unfailing good humor, generous motives and loyalty to high ideals and to his friends. Admired and respected by all conscientious students and loved by those who came into close contact with him, he helped greatly toward the establishment of high standards of scholarship and manhood in the student body.

In his death we lose a comrade whom we esteemed most highly, a generous and faithful friend.

S. Walter Ranson

Chicago,
June 24, 1915

FRATERNITAS MEDICORUM

The following appeal has been addressed by the distinguished committee whose names are appended to members of the medical profession. Every physician is entitled to membership in the Brotherhood (Fraternitas Medicorum = F.M.); there is no fee attached to this membership. However, in order to be able to maintain the organization, distribution of appropriate literature, etc., voluntary contributions will be welcome. Enrollment of membership as well as contributions are to be sent to The Medical Brotherhood, care of Dr. S. J. Meltzer, 13 West 121st Street, New York City.

AN APPEAL

To the men and women engaged in medical practise and the advancement of the medical sciences.

The present horrible war among civilized nations has brought out impressively certain sad facts; that although there are civilized *individual* nations, we are still very far from having a civilized humanity—there is an abyss between *intra*national and *inter*national morality; that, no matter how cultured and enlightened nations may be, they still settle their international differences by brute force, by maiming and killing their adversaries; and, finally, that the present high development of science and invention in individual nations only serves to make the results of this war more destructive than any other in history.

The war has demonstrated, however, one encouraging fact, namely, that among all the sciences and professions, the medical sciences and medical practise occupy an almost unique relationship to warfare, and that, among all the citizens of a country at war, medical men and women occupy a peculiar and distinctive position.

No discovery in medical science has been utilized for the purpose of destroying or harming the enemy. Medical men in each of the warring countries are as courageous, as patriotic, as any other citizens, and are as ready to die or to be crippled for life in the service of their country as any other class of their fellow countrymen. But their services, however, consist in ministering to the sick and to the injured and in attending to the sanitary needs. Furthermore, they often risk their lives by venturing into the firing line to bring the injured to places of safety and to attend to their immediate needs. *In these heroic and humanitarian acts friend and foe are treated alike.* Finally, the majority of the members of the medical profession and of the medical journals of the neutral as well as of the warring countries, abstain from public utterances that might be grossly offensive to any of the belligerent nations.

These facts—this advanced moral position in international relations which medicine and its followers are permitted to occupy in all civilized nations ought to be brought to the full consciousness of the men and women engaged in the medical sciences or in medical practise. Such a realization could not fail to have an elevating influence upon the medical profession itself, and would probably exert a favorable influence upon the development of international morality in general.

At the dawn of history, medical men were frequently also the exponents of philosophy and morals. In the middle ages, when knowledge became specialized, medical men more and more devoted their activity exclusively to medical practise. Because of its inefficiency at that time, medicine lost its prestige. In recent times, however, medicine is becoming an effective science; one marvelous discovery has followed another, and the efficiency of medical practise has been rapidly increasing. Medicine makes habitable to man hitherto uninhabitable parts of the world. It prevents disease; and, with increasing theoretical and practical efficiency, medicine is learning to alleviate and cure disease and injuries. Medical science and medical men have steadily risen in the esteem of civilized mankind. *May not the medical sciences and medical men become again the standard bearers of morality, especially of international morals?*

To accomplish these objects, it is proposed to organize as large and effective an association as may be possible, of men and women engaged in the medical sciences or in medical practise under the name of

THE MEDICAL BROTHERHOOD FOR THE FURTHERANCE OF INTERNATIONAL MORALITY

It is obvious that such a brotherhood could not exercise an important influence at once. But our modest expectation for prompt results should not prevent us from attempting *now* to take the first step in the right direction. Many important results have often had small beginnings.

A committee of physicians and medical investigators request you herewith to enroll as a member, and to declare your willingness to endorse and support the moral standard which the medical profession generally upholds when called upon to perform its patriotic duties in an international strife.

It should be expressly understood that it is not the object of the proposed brotherhood to influence the feelings and views of any one regarding the problems involved in the present war. It is desired merely to bring to the full consciousness of the members of the medical profession the exceptional moral position which all civilized nations, even while at war, *permit* and *expect* medical men to occupy, at least as long as they remain in the medical profession and act in this capacity. This consciousness can not fail to elevate the moral standards of physicians. Furthermore, after the close of the present war, the brotherhood could without doubt facilitate the reunion of the members of

the medical profession of all the nations which are now at war and increase good feeling among them. A humanitarian body such as the proposed brotherhood, if already in existence and ready for service, might and could be of the greatest usefulness in many ways.

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Dr. Albert P. Mathews, professor of physiological chemistry, University of Chicago, Chicago.

Dr. Ward J. MacNeal, director, New York Post-graduate Hospital, Medical School, New York City.

Dr. F. G. Novy, professor of bacteriology, University of Michigan, Ann Arbor.

Dr. Albert J. Ochsner, professor of surgery, University of Illinois, Chicago.

Dr. G. M. Piersol, editor, *American Journal of the Medical Sciences*, Philadelphia.

Dr. W. M. Polk, director, Cornell University Medical School, New York City.

Dr. W. A. Pusey, professor of dermatology, University of Illinois, Chicago.

Dr. Stewart Paton, neurologist, Princeton, New Jersey.

Dr. Richard M. Pearce, professor of experimental medicine, University of Pennsylvania, Philadelphia.

Dr. Joseph H. Pratt, Harvard Medical School, Boston.

Dr. J. J. Putnam, professor of neurology, emeritus, Harvard Medical School, Boston.

Dr. Howell T. Pershing, professor of neurology, University of Colorado, Denver.

Dr. David Riesman, professor of clinical medicine, University of Pennsylvania, Philadelphia.

Dr. M. J. Rosenau, professor of preventive medicine, Harvard Medical School, Boston.

Dr. Beverley Robinson, professor of medicine, emeritus, University and Bellevue Medical School, New York City.

Dr. B. Sachs, neurologist, Mt. Sinai Hospital, New York City.

Dr. P. A. Shaffer, professor of biological chemistry, Washington University Medical School, St. Louis.

Dr. C. G. Stockton, professor of medicine, Buffalo Medical College, Buffalo.

Dr. Thomas L. Stedman, editor, *Medical Record*, New York City.

Dr. Torald Sollmann, professor of pharmacology, Western Reserve University, Cleveland.

Dr. Allen J. Smith, professor of pathology, dean, University of Pennsylvania, Philadelphia.

Dr. Winford H. Smith, superintendent, Johns Hopkins Hospital, Baltimore.

Dr. Frank F. Simpson, Pittsburgh, Pa.

Dr. W. T. Sedgwick, professor of biology, Massachusetts Institute of Technology, Boston.

Dr. Mabel Ulrich, Minneapolis, Minnesota.

Dr. Ap Morgan Vance, Louisville, Kentucky.

Dr. Martha Wollstein, associate, Rockefeller Institute, New York City.

Dr. George B. Wallace, professor of pharmacology, University and Bellevue Medical School, New York City.

Dr. J. Whitridge Williams, dean, Johns Hopkins Medical School, Baltimore.

Dr. J. C. Wilson, professor of medicine, emeritus, Jefferson Medical College, Philadelphia.

Dr. Hiram Woods, professor of ophthalmology, University of Maryland, Baltimore.

Dr. Jonathan Wright, New York City.

Dr. H. Gideon Wells, professor of pathology, University of Chicago, Chicago.

Dr. Ray L. Wilbur, professor of medicine, dean, Leland Stanford Junior University, San Francisco.

Dr. Richard Weil, assistant professor of experimental therapeutics, Cornell Medical School, New York City.

THE PRODUCTION OF RADIUM IN COLORADO

Secretary of the Interior Lane authorizes the statement that the production of radium from Colorado carnotite ores by the Bureau of Mines, in connection with the National Radium Institute, has passed the experimental stage in its new process and is now on a successful manufacturing basis. He says:

The cost of one gram of radium metal produced in the form of bromide during March, April and May of the present year was $36,050, I am informed by Dr. Charles L. Parsons, in charge of the radium investigations of the bureau. This includes the cost of ore, insurance, repairs, amortization allowance for plant and equipment, cost of Bureau of Mines cooperation, and all expenses incident to the production of high-grade radium bromide. When you consider that radium has been selling for $120,000 and $160,000 a gram, you will see just what the Bureau of Mines has accomplished along these lines.

The cost of producing radium in the small experimental plant during the first few months of the bureau's activities was somewhat higher but not enough to seriously effect the final average.

The public, however, should not infer that this low cost of production necessarily means an immediate drop in the selling price of radium. The National Radium Institute was fortunate in securing through the Crucible Steel Company the right to mine ten claims of carnotite ores belonging to them and this was practically the only ore available at the time. Since then new deposits have been opened but these are closely held and according to the best judgment of the experts employed by the Bureau of Mines the Colorado and Utah fields, which are much richer in radium-bearing ores than any others known, will supply ore for a few years only at the rate of production that obtained when the European war closed down the mines. The demand for radium will also increase rapidly, for the two or three surgeons who have a sufficient amount of this element to entitle them to speak from experience are obtaining results in the cure of cancer that are increasingly encouraging as their knowledge of its application improves. A few more reports like that presented to the American Medical Association at its recent San Francisco meeting and the medical profession, as a whole, will be convinced of its efficacy. Under all the circumstances that have come to my knowledge it does seem to me that it behooves the government to make some arrangement whereby these deposits, so unique in their extent and their richness, may be conserved in the truest sense for our people, by extracting the radium from the ores where it now lies useless and putting it to work for the eradication of cancer in the hospitals of the Army and Navy and the Public Health Service.

The ten carnotite claims being operated at Long Park, Colorado, by the National Radium Institute have already produced over 796 tons of ore averaging above two per cent. uranium oxide. The cost of ore delivered at the radium plant in Denver has averaged $81.30 per ton. This included 15 per cent. royalty, salary of Bureau of Mines employees, amortization of camp and equipment and all expenses incident to the mining, transportation, grinding and sampling of the ore.

A concentrating plant for low-grade ores has been erected at the mines and is successfully recovering material formerly wasted. Grinding and sampling machinery has been installed at Denver and a radium extraction plant erected in the same city. The radium plant has now a capacity of three tons of ore per day, having been more than doubled in size since last February. Before that time that plant had been run more or less on an experimental scale although regularly producing radium since June, 1914. To July 1, slightly over three grams of radium metal had been obtained in the form of radium barium sulfate containing over one milligram of radium to the kilogram of sulfates. The conversion of the sulfates into chlorides and the purification of the radium therefrom is easily accomplished and with very small loss of material. Unfortunately, however, special acid-proof enamel ware, obtainable only in France, has not been delivered of sufficient capacity to handle the crystallization of the full plant production, so that a little less than half the output, or to be exact, 1,304 milligrams of radium element have been delivered to the two hospitals connected with the National Radium Institute. The radium remaining can be crystallized at any time from neutral solution in apparatus already installed, but the greater rapidity and efficiency of production of this very valuable material by the methods used have decided the Bureau of Mines to await the completion of apparatus now being built before pushing the chloride crystallization to full capacity.

The average radium extraction of all ore mined by the National Radium Institute has been over 85 per cent. of the amount present in the ore as

determined by actual measurement. The amount present in the ore has been found in fact to be essentially the same as the theoretical amount required by the uranium-radium ratio. The extraction figures for the last five carloads of carnotite treatment has shown a recovery of over 90 per cent. in each case.

A bulletin giving details of mining, concentration and methods of extraction is being prepared by the Bureau of Mines and will be issued early in the fall.

SCIENTIFIC NOTES AND NEWS

Dr. David Starr Jordan has been elected a member of the Royal Swedish Academy of Science at Stockholm, in appreciation of his work in zoology.

It is planned at Brown University to collect a fund to endow the library of the department of mathematics in honor of Professor Nathaniel F. Davis, who will retire from active service at the close of the present academic year, after having served Brown University for over forty years.

The University of Edinburgh has conferred the degree of doctor of laws on Professor W. A. Herdman, who holds the chair of zoology in the University of Liverpool, and on Professor Arthur Thomson, who holds the chair of human anatomy in the University of Oxford.

The Royal Scottish Geographical Society has awarded the Livingstone gold medal to Lord Kitchener in recognition of his work on the survey of Palestine and as director of the survey of Cyprus, as well as in recognition of his services to the state. The society's gold medal has been awarded to Dr. J. Scott Keltie, late secretary of the Royal Geographical Society, in consideration of his services to geographical science.

The medal and grant for 1915 of the South African Association for the Advancement of Science have been awarded to Mr. C. P. Lounsbury, chief of the division of entomology, Union Department of Agriculture.

The following is a list of recently elected honorary fellows of the Royal Society of Medicine: *British:* Sir R. Douglas Powell, Lord Moulton, Sir John McFadyean, Sir Francis Darwin, Robert Bridges, Lieutenant-Colonel Sir David Prain, T. Pridgin Teale, Sir John Williams, Professor E. G. Browne, Professor S. G. Shattock. *Foreign:* Professors J. Babinski, A. Chauffard, Jules Dejerine, M. T. Tuffier of Paris, and Dr. Paul Heger, of Belgium.

The Hanbury medal has been awarded to Mr. E. M. Holmes, curator of the Pharmaceutical Society's Museum, for his original research in the natural history of drugs.

On June 30, as we learn from *Nature,* Dr. Alexander Fischer de Waldheim, director of the Imperial Botanic Garden of Peter the Great at Petrograd, completed the fiftieth year of his scientific and administrative activities. The event was made the occasion of a ceremony with presentation of addresses in the hall of the herbarium at the garden. Dr. Fischer de Waldheim commenced his botanical career as docent at the University of Moscow, and later became professor of botany at the University of Warsaw. On the death of A. F. Batalin in 1897 he was appointed director of the gardens at Petrograd.

The committee on awards for scientific exhibits at the San Francisco meeting granted gold medals to the pathological departments of Stanford University and of the University of Michigan; to the Indiana State Board of Health, for its exhibit on a public health campaign; to Drs. C. C. Bass and F. M. Johns, of Tulane University, for their exhibit on pyorrhea alveolaris and malaria; to Drs. Claud A. Smith and J. Witherspoon, on hookworm; to the pathological laboratory of the New York Lying-in Hospital, on the demonstration of the cultivation of human tissue *in vitro;* to Dr. Martin H. Fischer, of Cincinnati, on newer experiments in the physiology and pathology of kidney functions, and to Dr. J. T. Case, of Battle Creek, on lantern slides illustrating Roentgen-ray studies.

The bronze thesis medal of the Science Club of the University of Wisconsin was awarded at commencement to Walter Pitz for a thesis on "The Effect of Elemental Sulphur and of Calcium Sulphate on Certain of the Higher

and Lower Forms of Plant Life." This medal is awarded annually to a senior in the University of Wisconsin for quality and quantity of research in preparing a thesis in physical or natural science, or pure mathematics, or their useful applications.

Dr. Goldwater, health commissioner of New York City, has resigned in order to resume his duties as superintendent of Mt. Sinai Hospital.

Edgar M. Ledyard, formerly assistant professor of entomology in the University of the Philippines, who has spent the last year in research work in the laboratory of parasitology of the University of California, has been appointed director of the Agricultural Department of the United States Smelting Company, Salt Lake City, Utah.

Colonel William Hunter, M.D., assistant physician to Charing Cross Hospital; Lieutenant-Colonel G. S. Buchanan, M.D., first assistant medical officer to the local government board; Lieutenant-Colonel Andrew Balfour, C.M.G., director of the Wellcome Bureau of Scientific Research, and Lieutenant-Colonel Leonard Dudgeon, F.R.C.P., lecturer on general and special pathology at St. Thomas's Hospital, have gone to the Dardanelles, as an advisory committee to assist the British Royal Army Medical Corps in dealing with epidemics.

The St. Louis University has fitted up an expedition to make a study of tropical diseases and biology in British and Spanish Honduras. The party which left New Orleans on July 21, was composed of the following: John P. Coony, Ph.D., S.J., professor of chemistry; E. N. Tobey, M.D., instructor in tropical diseases, and A. M. Schwitalla, S.J., A.M., a student in biology.

UNIVERSITY AND EDUCATIONAL NEWS

Mr. C. W. Dyson Perrins, who gave £5,000 toward the construction of the University of Oxford chemical laboratory which is nearing completion, has lately offered to present to the university a further sum of £25,000, of which £5,000 is to be applied to the equipment of the laboratory, and the remaining £20,000 is to form a permanent endowment fund for maintenance of the laboratory and for the encouragement of research and instruction in chemistry.

George Peabody College for Teachers has received $8,500 from Miss Eleanor Cuyler of New York City and Mr. Thos. DeWitt Cuyler of Philadelphia, for equipping the Jesup Psychology Laboratory. This amount of money is to be spent for furniture, laboratory equipment and psychological publications.

Professor H. S. Jackson, of the Oregon Agricultural College, has accepted the position of head of the botanical department of the Agricultural Experiment Station of Purdue University, Lafayette, Indiana, to take effect September first, as successor to Dr. J. C. Arthur, who retires as a beneficiary of the Carnegie Foundation for the Advancement of Teaching.

Dr. E. W. Sinnott, of the Bussey Institution, has been appointed professor of botany and genetics at the Connecticut Agricultural College.

At Yale University, Reynold A. Spaeth, Ph.D. (Harvard, '13), instructor in embryology at Clark University, has been appointed instructor in biology in Yale College.

The following appointments have been made at the Massachusetts Institute of Technology: George Owen (M. I. T., '94), assistant professor of naval architecture; Royal M. Frye, A.B., instructor in physics; Charles H. Calder, Horatio W. Lamson and Joseph C. MacKinnon, assistants in physics; Elwyn E. Snyder, Jr., assistant in industrial chemistry.

At Rutgers College research assistants have been appointed as follows:

Roland E. Curtis, B.S. (Oregon), soil bacteriology.
F. E. Allison, B.S. (Purdue), M.S. (Iowa State), Amos Phos fellow.
Selman A. Waksman, B.S. (Rutgers), soil bacteriology.
Carl R. Fellers, B.S. (Cornell), soy bean.
William S. Porte, B.S. (Rutgers), plant physiology.
Orville Schultz, B.S. (Iowa State), plant breeding.
W. H. Martin, B.S. (Maine), plant pathology.
W. S. Krout, B.S., M.A. (Ohio State), plant pathology.
Homer E. Carney, B.S. (Miami), botany.

A. C. Foster, B.S. (Alabama Polytechnic), botany.

Franklin O. Church, B.S. (Rutgers), hydraulic engineering.

F. P. Schlatter, B.S. (Pennsylvania State), cranberry investigations.

DR. FRANCIS ARTHUR BAINBRIDGE, of the University of Durham, has been appointed to the University of London chair of physiology tenable at St. Bartholomew's Hospital Medical School.

DISCUSSION AND CORRESPONDENCE

LOSING THE ADVANTAGES OF THE BINOMIAL SYSTEM OF NOMENCLATURE

THE communication from Dr. F. B. Sumner which appeared in SCIENCE for June 18 last on the subject of saving the genus as a category of zoological classification, is certainly a timely one, and expresses views that are by no means confined to its author. It will require but little examination of the facts to lead to the conclusion that not the enforcement of the law of priority, but unrestricted splitting of genera, is responsible for most of the confusion and instability which characterize zoological nomenclature to-day, and makes it a source of inconvenience and uncertainty, demanding from scientific men much profitless labor, and expenditure of mental energy sufficient to bring about important advances in science if it could be turned into some useful channel.

Few zoologists ever stop to think how far we are getting away from a real binomial system of nomenclature. It is true that scientific names of animals still consist of two words, but only in a minority of cases does the first term of the binomial have any real meaning to us, or suggest ideas of a much broader and more comprehensive character than the second one. The genus name has become little more than a mere prefix to, or part of, the species name. The addition of a few more letters or syllables to the latter (to prevent confusion of organisms which have chanced to receive the same specific designation) would serve the same purpose. We learn generic names, if we learn them at all, by mere acts of memory, and we use them because we find them in the latest monographs and might be thought not up to date if we did otherwise, but what the distinctions are between these multitudes of closely allied genera we rarely stop to inquire. Indeed, if we do have interest enough to look up such points, the slight importance and complexity of the distinctions are apt to surprise and discourage us, and convince us that we had better take the specialist's word for them, and spend our time and labor in some more useful way. In short, though our classification is binomial in form, it is only very imperfectly so in effect.

Even within the memory of some scientific men living to-day, the system in use did still afford the practical advantages which secured the universal adoption of the system of Linnæus. The recognized genera, though even then being multiplied to an inconvenient extent, were still in a majority of cases separated by sufficiently well-marked characters and not as yet too numerous to enable the professional zoologist and even the more serious amateur students of the science to recognize by name and classify a large proportion of the genera, and to recall some of their more important characters. A genus name had in those days a real meaning to some others besides the specialists in the class of animals to which the genus happened to belong.

It would be a mistake to maintain that zoological classification has suffered through the recognition of these minor subdivisions. They exist in nature, and should have a recognition commensurate with their importance. The older and more comprehensive genera are now in many cases treated as subfamilies or families. Classification has gained in exactness and truthful representation of the facts, but through our neglect to keep the first term of our scientific names comprehensive in its application, and easily distinguished and remembered in its meaning, we have allowed our nomenclature to lose most of the practical advantages and conveniences of the Linnæan system.

Unfortunately, specialists, as Dr. Sumner has hinted, are only too apt to study their specimens till they see only differences and lose sight of much more important resemblances,

and hence to commit in their own works the offenses that they find fault with in the works of other authors. They should sometimes endeavor to look upon their subject from the point of view of the general zoologist, and get a more correct perspective of the relative importance of characters than can be obtained if their ideas run too much within the narrow limits to which the study of restricted groups tends to confine them. If specialists will take the lead in reducing to subgenera or sections many of the genera now recognized, other zoologists will be only too glad to follow them. Such a course would not for a moment require the abandonment of those genera as divisions of classification, nor necessarily indicate the admission of any change of view as to their intrinsic importance; it would be merely a question to be decided on the basis of obtaining a nomenclature practical for zoologists in general. As it is now, our nomenclature is adapted for specialists only, and for each specialist only for his own particular field of study. As far as the rest of the animal kingdom is concerned, he is in the same position as a general student of zoology, and finds the existing nomenclature as inconvenient as every one else does.

One common practise seems to be especially illogical. That is the attempt to break up well-defined genera simply because they contain a large number of species. Such genera exist in nature, as well as many genera with a few or with but one species, and this must be the case in our classification also if it is to be true to nature. It is claimed that large genera are "inconvenient," but in such cases the inconvenience is not in the classification, but in nature itself, which has evolved a large assemblage of closely allied forms, and it is often made worse rather than better by the attempt to distinguish genera which have no real dividing limits.

The writer is inclined to question whether Dr. Sumner has gone quite far enough in recommending subgenera as substitutes for many of our present genera. Some of the latter hardly deserve even that low rank. A subgenus receives a scientific name of the same form as a genus name, and affords a standing temptation for the next specialist who makes a more minute division, to treat it as a genus, thereby changing the scientific names of all the species involved. Even if this never happens, scientific literature is burdened with a new technical name which adds its weight to the already excessively large proportion of zoological subject-matter which consists of mere names of things, in distinction to real knowledge about animals. Names and technical words we must have, but whether we do it consciously or not, we use mental energy in learning and remembering and using them, or in looking them up in books. If neither necessity nor frequent and general usefulness justifies their existence they should be done away with, or, better still, never coined. The best carpenter or machinist neither needs nor desires the largest possible set of tools, and hesitates to encumber himself with extra ones which he has no real need of, and science would probably be as well off with fewer technical words.

A method that has often been used and proved a satisfactory one for naming unimportant groups is that of designating them by their best known or first described species. Such a system has been applied to the minor divisions of large genera, as *Unio*, by Simpson in his well-known synopsis of the Naiades, where he speaks of the "group of *Unio gibbosus*," "the group of *Unio littoralis*," etc. Not only are no new words coined, but to those with some familiarity with the genera in question the groups are better understood than if they were called by some arbitrarily formed and no less arbitrarily applied combinations of Greek or Latin roots and suffixes. Simpson used this method only for assemblages of very nearly allied species, but it might well be extended to many groups now treated as genera or subgenera.

If instead of coining new technical words, simple and logically formed combinations of more or less familiar ones were more generally employed, we would be saved the necessity of learning and remembering, looking up and explaining hundreds if not thousands of needless words and names, and have a correspond-

ingly greater part of our time left for acquiring and employing really useful knowledge, and the purposes and results of scientific investigation would be understood and appreciated by a larger part of the public than is now the case.

WILLARD G. VAN NAME
NEW YORK STATE MUSEUM

AMERICAN SANITATION

TO THE EDITOR OF SCIENCE: The writer has just finished reading Dr. Ford's most interesting article on "American Sanitation," in your issue of July 2, and wishes to endorse heartily the plea therein contained for more extensive and better training in public health. The writer feels, however, that he must differ with Dr. Ford as to the wisdom of excluding all but physicians from participation in health work. Dr. Ford evidently assumes that there is no essential difference between community hygiene and personal hygiene, and that a thorough medical training, with its time-consuming studies of anatomy, histology, obstetrics, materia medica, etc., is essential before undertaking special work along the lines of sanitation, or the protection of the community from disease.

The present writer holds no brief for the ordinary engineer in positions of high responsibility in general health work, but he can not help feeling that a well-trained sanitary engineer would distinguish his incumbency of the health officership of a town, about as well as an eye and ear specialist would do. In fact, the chances are that neither would be conspicuously successful.

The ideal health officer should be neither an M.D. nor a C.E. but should be an expert in community hygiene, such expertness combining a knowledge of both branches (and some others). It should be possible for a young man desirous of entering the field of public health to secure training for that service without being compelled to undertake the study of a great many medical subjects which have to do with curative rather than with preventive medicine; and also without having to learn about highways, railways and framed structures. He should, upon completion of such a course of training, be thoroughly conversant with the causation and transmission of disease; and have enough engineering training to enable him to look upon problems in municipal sanitation with that sense of perspective which is found more highly developed among civil engineers than among physicians.

An amusing story illustrating that lack of quantitative appreciation, or perspective is vouched for by one of the writer's professional friends. A practising physician in one of our large cities sent a communication to the health commissioner in which he recommended the addition of some mild laxative to the city water to counteract the baleful effects of the coagulants applied previous to filtration. Of course, it is to be understood that this is recognized as an extreme case, but in the course of ten years' experience as a sanitary engineer, the writer has heard many decidedly puerile things said by physicians who pretended to some knowledge of sanitation.

WM. T. CARPENTER
BROOKLYN SEWAGE DISPOSAL
EXPERIMENTAL STATION

ANIMAL MALFORMATIONS

TO THE EDITOR OF SCIENCE: Referring to the communication on "a chicken with four legs" in SCIENCE, page 90, I would say, lest the malformation should be considered rare, that we have in this museum quite a number, fourteen from the chicken alone, showing various degrees of the malformation; also from the duck and turkey, and from some higher animals as the dog, pig and kitten. Technically the malformation is known as dipygus or preferably as dipygus parasiticus.

D. S. LAMB
U. S. ARMY MEDICAL MUSEUM,
WASHINGTON, D. C.

THE LONG COST OF WAR

TO THE EDITOR OF SCIENCE: The writer is interested in gathering material bearing on the eugenics of war and militarism. It is obvious that these influences tend to weaken a nation through the destruction of those physically the best and through the debarring of

the soldier from honorable parenthood. In addition to abundant records from Europe and America, we have the following facts from Japan.

The war between China and Japan occurred twenty years ago. It involved the destruction of a large number of picked men of Japan and a corresponding reduction in the virility of the nation. The effects of the loss on the succeeding generation can not be felt until the children born in 1895 attain their majority. These results can be measured only in the reduced stature of the incoming conscripts and in the proportion of exemptions from military service. "Like the seed is the harvest." The new generation takes the quality of those men and women who were its actual parents. Those whom war has destroyed, in general the stronger and the best developed physically, are not represented.

According to the *Asahi* of Tokyo, as translated in the *Japan Chronicle,* the number of available conscripts in Tokyo for this year is 9,235, instead of 9,981. For a number of years there had been a steady increase of about 800. This falling off of 1,546 marks a decrease of over 16 per cent. In Kanda, the most densely populated ward of Tokyo, the decrease was 22 per cent.

In the whole nation, a slight increase of conscripts has taken place, 482,965 as against 472,147 of 1914. But this rate of increase (9,000) is only from thirty to fifty per cent. of the normal, which for years has ranged from 20,000 to 30,000.

More important than the reduction in numbers is the lowering in quality. In Kanda in 1914, twenty-four per cent. of the conscripts were passed as "strong," while in 1915, the percentage was thirteen per cent. (83 out of 635, instead of 194 out of 813). A much larger percentage of those sent to the barracks were of the "average" class.

The birth-rate in Japan, as in every other nation, declined in time of war, to rise again at its conclusion.

This decline of physique is a matter of concern to the military authorities of Japan, but they optimistically hope that it is of a temporary nature. The *Asahi* concludes that "most of those who underwent conscript examinations this year were born during the war and therefore are sons of those too old or too weak to go to the front, and so it is no surprising thing if the conscripts of 1915 are of exceptionally delicate constitution."

David Starr Jordan

July 24, 1915

SCIENTIFIC BOOKS

Key to the Families of North American Insects. By Charles T. Brues and A. L. Melander. Boston, Mass., and Pullman, Wash., published by the authors, 1915.

Most modern works on entomology contain keys or tabular synopses, intended to facilitate the determination of families, genera and species. It is the experience of those who have classes in entomology that these keys are on the whole unsatisfactory, being frequently incomplete, incorrect or unintelligible. The most noteworthy exception is found in Williston's "Manual of North American Diptera" (1908), which, considering its scope, could hardly be improved. One who has constantly used Williston's book for a number of years becomes convinced that it is possible to prepare keys which will in nearly every case enable the student to determine the genus of the insect before him, especially when he has also the aid of numerous outline figures. It is really astonishing how soon a clever student will learn to use works of this kind; at Boulder we find that students using an illustrated table of Rocky Mountain bees can frequently determine correctly as many as four genera in an hour, in spite of the fact that the insects and the kind of work are new to them. Exceptional students do even better than this.

The method having proved so satisfactory, Professors Brues and Melander thought it worth while to prepare a key to all the families of North American insects, illustrated, like Williston's book, with many outline figures. Thus we have for the first time a complete synopsis of the families, whereby the student may find the place in the taxonomic system of

any insect he happens to have obtained. In preparing this key, the authors have taken advantage of all previous work which appeared serviceable, added to their own extensive knowledge of a number of groups, so the result is probably not far from the best attainable in the present state of our knowledge. The book will be invaluable to all students of entomology, and will be in constant use in every entomological laboratory. The details of insect classification are not so well established that it is possible to present a system which will be universally approved. In the present case we recognize a number of improvements over arrangements previously current, but we must protest against the uncritical adoption of the system of Handlirsch. It is actually proposed to recognize five classes of insects, the additional four being made out of the Aptera, one of them containing the recently discovered Protura. Then, again, the old order Orthoptera is divided into a long series of orders, placed in two subclasses. The reviewer has not critically reconsidered the whole subject to determine exactly what support may be found for all these changes, but neither has any one else in this country, so far as we know, for it would involve many months or years of intensive labor, with access to very large collections. The reviewer has however had much occasion to use Handlirsch's great work "Die fossilen Insekten," in which the new classification appears, and has come to a clear estimate of its merits and faults. It is a wonderful compilation, showing enormous industry and great ability, and will always rank as a classic in the literature of entomology; but in detail, and especially in its innovations, it is not to be trusted, the taxonomic arrangements set forth with so much assurance being often based on very inadequate grounds or imperfect knowledge. It may well be that this author has been taken more seriously than he himself intended. A new classification, even if faulty, is of value if it stimulates thought and is received in a critical though friendly spirit; to adopt it *en bloc* without criticism is in a sense to do an injustice to the eminent author.

Only frequent use will show how serviceable the key is in all its details. Undoubtedly many little changes will be required in the next edition. As the authors observe, the families are not of equal rank, and it seems impracticable to make them so. All the scale insects and mealy-bugs are still Coccidæ, all the ants are called Formicidæ, while the bees are divided into twelve families.

T. D. A. COCKERELL
UNIVERSITY OF COLORADO

ON THE ACOUSTICS OF THE CHAPEL OF ADELBERT COLLEGE

IN SCIENCE of November 14, 1913, was published a short account of experiments made to determine the effect of a sounding board on the acoustic qualities of the chapel of Adelbert College. The sounding board, constructed at the suggestion of the architect of the building, and in accordance with his specifications, was of the canopy type, about six feet in diameter, and suspended about two feet above the head of the speaker. An investigation showed, as was not unexpected, that the sounding board was without noticeable effect, and it became necessary to try other remedies.

A sufficiently detailed description of the interior of the chapel is given in the previous article, and need not be repeated. The ceiling of the building is of wood, the walls are in part of stone, and in part of plaster laid directly upon the stone without lath or furring.

There was no evidence, as was before stated, of special or local echoes. The difficulty was plainly one of excessive reverberation, due to the insufficient absorbing power of the walls and ceiling. It was evident that the only effective remedy was to cover a portion of the walls with highly absorbent material, after the manner devised by Professor Sabine, of Harvard University. The generosity of the donors of the chapel provided the necessary means; the work was intrusted to an "acoustic engineer," a former student of Professor Sabine's, and Mr. Sabine himself was good enough to aid with counsel and suggestion.

Calculation showed that a reasonably effective treatment might be obtained by covering the ceiling and the upper part of the walls

down to the springing of the window arches with a specially prepared felt.

The felt as actually applied was two inches thick on the ceiling, one inch thick on the side walls. The work was carried out with admirable efficiency and carefulness. The appearance of the chapel was practically unchanged, so that no one, unaware of the treatment, would have guessed that any application of the kind had been made.

Experiments extending over one college year were made to test the effectiveness of the arrangement.

A college chapel service, where attendance is required, affords a unique opportunity for a study of this kind. Five regular services weekly are held in the Adelbert College chapel. One of these is a musical service; the other four generally include a short address on some practical or ethical subject. The services are conducted by a number of clergymen from the city, each of whom officiates in general all the four days in a given week. It is possible, therefore, for an observer to listen to the same speaker for four successive days. The audience is practically the same each day, and the general conditions are nearly constant, so that the observations made on successive days are comparable to a satisfactory degree.

The experiments consisted simply in listening to a speaker on successive days, from different parts of the auditorium, and noting down in each case the percentage of the words spoken which were clearly understood. Effort was made to consider only words which were definitely heard, excluding as far as might be those gained by association from the context. Previous experiments, in connection with the sounding-board, had given some facility in this kind of work. Of course, only a rough approximation is possible, yet the margin of error is perhaps less than would be at first supposed. The attention is fixed, not on the number of words understood, but on the number missed. It is easy to distinguish approximately between the loss of one word in five, one in ten, one in twenty; these correspond to an audibility of 80, 90 and 95 per cent., respectively. 95 per cent. means excellent hearing, 90 per cent. is fair, but if the number of words heard is only 80 per cent. of the whole, the hearing is positively poor, and below this runs rapidly into unintelligibility. Perfectly satisfactory hearing, clear and sharp, without effort or close attention, is rated at 100 per cent.

Four seats were chosen as places of observation, one in the front row of the gallery at the back of the chapel, perhaps ninety-five feet from the pulpit where the speaker stood, three on the floor, seat AA, immediately under the front edge of the gallery, about ninety feet from the speaker, seats V and Q, respectively seventy-five and fifty-five feet from the speaker. The observer sat on successive days in each of these seats in rotation, making notes as suggested above.

The chapel was treated with the absorbent felt during the summer vacation of 1914. The experiments began in February, 1914, while the chapel was in its original condition, while the second set, after the treatment of the walls, extended from the latter part of September, 1914, to the end of February, 1915, the whole including two college semesters.

The relative number of words heard in the case of each speaker having been evaluated as closely as possible, the results were averaged for each position of the hearer. For example, in the seat AA, ninety feet from the speaker, 25 experiments were made during the first semester, varying in intelligibility from 10 per cent. to 95 per cent. The average of all the speakers was 71 per cent. This means that on the average more than one word in four was missed by the hearer. In almost every case the necessary attention was recorded as "careful" or "strained." Listening was wearisome, and it was often impossible to follow intelligently the purport of the address.

In the second semester, sitting in the same position, 28 speakers were heard. The average audibility was 91 per cent. The attention given was recorded as "easy" in about half the cases, as "careful" in the others. In no case was a tense or strained attention needful.

The improvement in hearing was greatest, of course, in the case of those who were heard with difficulty, though in all cases the gain was

marked. One speaker in particular, as the result of several hearings, in the first half-year was rated at 10 per cent., in the second at 76 per cent.

Of the different speakers, six were heard in both of the semesters, and are thus more directly comparable than the others. Their average for the first semester was 64 per cent., for the second, 92 per cent., that is, while during the first semester more than one word out of every three was unintelligible, only about one in twelve was unheard in the second.

The effect was even more striking in seat V. Before the treatment of the chapel the average audibility was 71 per cent., exactly the same as at the greater distance, showing that the advantage gained by a somewhat nearer approach to the speaker was completely nullified by the disturbances from reverberation. The attention, as in the seat AA, was careful or strained. After the treatment the average audibility rose to nearly 96 per cent., nearly perfect hearing, and the attention in most cases was noted as easy.

In seat Q, about fifty-five feet from the speaker, the audibility rose from an average of 95 per cent. in the first semester to 100 per cent. in each separate case in the second.

The results are summarized below for more easy comparison.

AVERAGE OF ALL SPEAKERS

Seat	First Semester. Per Cent.	Second Semester, Per Cent.
AA	71	91
V	71	96
Q	95	100

The seat in the gallery gave exactly similar results, but the number of experiments made in this seat was so small that the averages are not included in the table.

The condition of the auditorium at present is satisfactory. It is quite possible that a slight further reduction of reverberation might be made with advantage to the spoken word, but the effect of music, which forms an important part of the uses of the building, would be correspondingly injured.

It may be worth while further to remark that the calculations as to the effect of reverberation could have been as well made, plan and materials being given, before the erection of the building as afterward. It is a pity that architects still construct buildings of this kind without giving careful attention to their expected uses, trusting to good fortune for acoustic fitness which might easily and certainly be insured in advance.

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SPECIAL ARTICLES

TWO COLOR MUTATIONS OF RATS WHICH SHOW PARTIAL COUPLING

In the *American Naturalist* for February, 1914, Castle described two yellow-coated varieties of the Norway rat (*Mus norvegicus*) which had recently been discovered in England, and both of which had been found to behave as Mendelian recessive characters in heredity. One of these was called "pink-eyed yellow," the other "black-eyed yellow." A more appropriate name for the latter would be "red-eyed yellow" (which we shall hereafter use), since the eyes in this variety are not as dark as in wild gray or tame black rats, but the red blood of the eye shows through, particularly when the animal is young, giving the eye in a favorable light a reddish tinge.

Upon crossing the two yellow varieties with each other, we found them to be complementary. The F_1 young obtained were none of them yellow, but were all either gray or black coated; yet it should be noted that they were in no case as dark as ordinary gray or black rats. Nevertheless F_2 young with coats of normal intensity were later obtained, so that the paleness of the F_1 young was evidently due rather to their being heterozygous for the two complementary factors, than to any failure of one variation completely to supply what was lacking in the other.

Each of the yellow varieties was also found to be different in nature from ordinary albinism, as seen in white rats, since when it was crossed with albinos it produced only fully

pigmented (gray or black) rats, which when crossed with each other produced an F_2 generation consisting of approximately 9 gray or black rats to 3 yellows, and 4 albinos, a typical dihybrid result.

But the most interesting aspect of the two yellow variations is their apparent "negative coupling" or mutual "repulsion," a phenomenon first discovered by Bateson and Punnett in plants, but since observed in insects by Morgan and Tanaka. This repulsion, in the case of the two yellow variations of rats, is incomplete, as is true in most recorded cases of repulsion, and it indicates, if we adopt Morgan's manner of explaining it, a location near together in the germ-plasm of the respective determiners or "genes" for red-eyed and for pink-eyed yellow.

The evidence for this partial repulsion is as follows: When the F_1 gray or black rats, obtained by intercrossing the yellow varieties, were themselves intercrossed, they produced an F_2 generation which contained 102 gray or black young, 55 red-eyed yellows, and 43 pink-eyed yellows.

To ascertain the gametic composition of the yellow F_2 animals, (1) the extracted red-eyed yellows were mated with yellows of the pure pink-eyed race, and (2) the extracted pink-eyed yellows were mated with pure red-eyed yellows. Twenty-eight test matings of the first sort have been made and twenty-seven of the second sort, with the following results.

In 20 matings, extracted red-eyed yellows mated with pure pink-eyed yellows have produced only black-eyed young (grays or blacks), while in the remaining 8 matings both black-eyed young (grays or blacks) and pink-eyed young have been produced. The red-eyed parent, in the former type of mating, must have lacked altogether the gene for pink-eye, while in the latter type of mating it must have been heterozygous for pink-eye. If we designate the (recessive) gene for red-eye by r and the (likewise recessive) gene for pink-eye by p, then the F_2 red-eyed yellows tested must evidently have been of the two types rr (20 cases) and rrp (8 cases), respectively. The former type, when mated with pure pink-eyed animals (pp), would produce only double heterozygotes (pr), whereas the latter would produce either double heterozygotes (pr) or homozygous pinks heterozygous for red-eye (ppr). On the theory of probability, if red-eye and pink-eye are produced by wholly independent genes, we should expect animals of the former type to be only half as common as animals of the latter type in a population of extracted (F_2) red-eyed yellows, *but observation shows them in this case to be more than twice as common!* Hence there is a strong presumption that red-eye and pink-eye depend upon genes not wholly unconnected with each other. This presumption is strengthened by the results obtained by testing the extracted F_2 pink-eyed yellows by mating them with pure red-eyed yellows. Twenty-seven such animals were tested, of which 19 produced only black-eyed young (grays or blacks), while 6 produced both black-eyed (gray or black coated) and red-eyed (yellow) young, and 2 others produced only red-eyed (yellow) young.

All the pink-eyed F_2 animals tested must have been homozygous for pink-eye (otherwise they would not have shown pink-eye), but as regards the possession of red-eye it is evident that conceivably they might (1) lack it altogether, (2) be heterozygous for it, or (3) might be homozygous for it, conditions which would be expressed by the formulæ pp, ppr and $pprr$, respectively. Animals of the first sort (pp), if mated with pure red-eyed animals, should produce only black-eyed young (grays or blacks, the observed result in 19 cases); animals of the second sort (ppr) should produce some young black-eyed and others red-eyed (the observed result in 6 cases); animals of the third sort ($pprr$) should produce only red-eyed yellow young, an expectation realized in 2 cases. The chance expectations for the occurrence of these three sorts of results are as 1 : 2 : 1; the observed occurrences are widely different, viz., 20 : 6 : 2.

If the repulsion between the two yellow variations were complete, no F_2 individuals of classes 2 and 3 (ppr and $pprr$) would be formed, but all F_2 pink-eyed yellows would be of class 1 (pp). The fact that classes 2 and 3 are

formed but are much *smaller* than expected shows that *partial* repulsion exists between the two yellow variations. In the origin of the 55 yellow rats which have been tested, 110 gametes were involved. Inspection of the results shows that in 92 of these gametes the factors for red-eye and pink-eye remained apart, as they were originally; but in 18 of them a cross-over must have occurred producing a gamete which contained both factors. This ratio of 92 unchanged to 18 cross-over gametes (or 5.1 to 1) among the gametes which produced the yellow rats, should give nearly, though not quite, the gametic ratio among *all gametes* produced by the F_1 rats. This true gametic ratio may be shown by the foregoing figures to be about 4.6 to 1 and the per cent. of cross-overs to be about 18.

Animals of class 3 (*pprr*), homozygous for both kinds of yellow, should produce gametes in which these two characters would show positive coupling instead of repulsion. This matter is now being investigated with the idea of finding a quantitative expression for the strength of the coupling and comparing it with the strength of the repulsion already demonstrated.

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TOXICITY AND MALNUTRITION[1]

The concept denoted by the word "toxicity" contains an element essentially physiological in its nature and describes primarily not so much a chemical property of a given substance as the result of a chemical reaction of this substance with one or more constituents of a given organism. Thus the effects produced by the chemical substance on the organism are obviously due to the chemical properties both of the substance itself and of the tissues of the organism. Hence, while derived in part from the chemical properties of the substance, toxicity does not exist apart from the organism and can be asserted of any given substance only after fitting experiments have been carried out on the organism in question. In contrast to this property, the purely chemical properties, such as acidity or alkalinity, exist apart from any relation to the organism. When a given chemical substance possessed of specific properties comes in contact with an organism which of course is essentially made up of substances having likewise definite chemical properties, the reactions which follow in accordance with the laws governing chemical behavior are capable of description by means of chemical terms, but from the standpoint of the organism a physiological result has occurred defined not in terms of ions and molecules, but in terms of function. When, as a result of the chemical reaction, the organism is so modified as to cause the non-performance or imperfect performance of function a more or less marked physiological injury is recognized. If the injury involves sufficiently important functions and the reaction is irreversible, death results. Should functional activity be impaired only in nonessential particulars or should the reaction be reversed, life may persist in spite of permanent injury or recovery may take place. If the arrest or derangement of function is sufficiently thorough and prompt, the organism is said, in popular phrase, to be "poisoned" and the chemical substance entering into the disturbing reaction is said to be a "toxic" substance. In view of these considerations there seems to be no scientific ground for limiting the term "toxicity" to the popular conception.

"Toxicity" results in functional impairment due to chemical reaction and, accurately speaking, is more a matter of kind than of degree. If this impairment proceeds to the point of death there might seem to be a basis for distinction between this result and that of a less serious injury not so terminating. However, if death takes place indirectly and remotely through secondary changes initiated by the chemical reaction, the organism would still have been "poisoned." If functional injury, however slight and remote, should follow from the chemical reaction, it would still be in kind a "toxic" action.

[1] Published by permission of the Secretary of Agriculture.

The terms "toxic" and "poisonous," as used popularly in characterizing chemical substances, are subject to still another consideration. Substances like corrosive sublimate, copper salts, hydrochloric acid and phenol, are popularly called "toxic" substances because, in concentrations familiarly used, they produce such marked chemical reactions in organisms as to cause serious impairment of function and perhaps death. It should be borne in mind, however, that these substances lose their ability to act toxically on sufficient dilution, and even the so-called harmless chemical agents when sufficiently concentrated, if still soluble, become harmful. The question of toxic action, therefore, comes down finally not only to a matter of the chemical properties of substances, but equally to a question of the concentration of the solution in which they encounter the organism. It would follow that perhaps all substances acting singly are potentially toxic.

It might seem that water, at least, would escape the suspicion of being "poisonous." Of course, pure water is practically unknown to biology and little can be asserted concerning its action on organisms. When this substance is referred to, distilled water, a dilute solution of various substances, is usually meant. The work of a host of investigators on distilled water has led to a great variety of results, a fact due on the one hand, doubtless, to the great variation in the water used, and, on the other, to the varying susceptibility of the experimental organisms employed. It has, however, been repeatedly shown that very minute traces of salts are able to profoundly modify the physiological properties characteristic of highly purified water.

It has been shown that distilled water withdraws small quantities of electrolytes from various organisms of both plant and animal origin, with the result that as this process advances, the water becomes an increasingly concentrated solution of ions. The ability of *Fundulus* eggs to resist the action characteristic of water rendered in a scientific sense even approximately pure, as claimed by Loeb, seems to be very unusual. It would be of interest to know accurately what the ion concentration of the distilled water used in these investigations might have been at the beginning of the experiment and after it had been occupied by the *Fundulus* eggs.

If toxicity is indicated by functional derangement due to chemical reactions, then clearly nothing can be toxic in its action that can not produce chemical change in the organism. In other words, mere absence can not furnish a ground for charges of toxicity against any substance. If the solution from which a necessary substance is lacking causes the development of toxic properties (*i. e.*, functional derangement due to chemical modifications produced in the organism by the external medium) the reaction causing the derangement must proceed from the substances in position to affect the organism. Hence, incomplete nutrient media or unbalanced solutions, both producing functional derangement, bring about this effect through the reactions performed by the substances present, certainly not by those not present. Perhaps the most satisfactory approach to the situation is seen through the relation supposed by Loeb and others to exist between ions and proteins in the living organism. For normal functioning certain affinities in the proteins of the organism must be occupied by certain ions in a rather definite way. When one such ion is lacking to the medium, the affinities normally occupied by it are satisfied in a chemical way by ions present without, however, satisfying the corresponding physiological requirement. While, therefore, the absence of a necessary ion gives the opportunity for the harm-bringing reaction to take place, the actual damage is wrought within the cell by constituents actually there present. Thus, a medium characterized as deficient or unbalanced becomes actively injurious through the effects produced by the ions that are present, and malnutrition, starvation, or even a more violent type of chemical injury may appear.

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